

# INTELLECTUAL DISABILITY AND PSYCHIATRIC DISORDERS AS EXCLUSION CRITERIA IN RANDOMIZED CONTROLLED TRIALS (RCT)

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## SUMMARY

People with intellectual disability or psychiatric disorders are commonly excluded from Randomized Controlled Trials (RCTs) because of explicit exclusion to the trials or because of inaccessible research protocols. We analyzed the exclusion rate of persons with cognitive impairment, psychiatric disorders and inability to give informed consent in interventional RCTs about the first 10 causes of global DALYs (disability-adjusted life-years) according to the Global Burden of Disease Study (GBD) utilizing the website Clinicaltrials.gov. A total of 2809 studies in the 10 selected categories were reviewed. "Cognitive impairment" was present in 488 (17.4%) studies, "Behavioural and psychiatric disorders" was present in 616 (21.9%) studies, "Inability to grant informed consent" was present in 498 (17.7%) studies and the three explicit criteria were present, alone or in combination, in 1076 studies (38.3%). Other disability-related exclusion criteria were considered to be implicit exclusion criteria and were present in 1233 (43.9%) studies. A judgement was made on the correlation between the exclusion criteria and the primary objectives of the studies analyzed. The low level of representation of people with disabilities in RCTs, in addition to being an ethical problem, is a limitation of scientific knowledge because it considerably reduces the external validity of a significant part of medical research. There is a need to review the way scientific research designs are constructed, seeking to promote greater inclusiveness of people with disabilities.

**Key words:** intellectual disability – psychiatric disorders – exclusions criteria – Randomized Controlled Trials

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## INTRODUCTION

Randomized Controlled Trials (RCTs) are considered the most reliable method to provide scientific evidence of efficacy of new drugs and interventions and their results lead to changes in medical practice (Van Spall et al. 2007)

An RCT must have a good internal validity, that is the extent to which it is able to establish a cause and effect relationship between a treatment and an outcome and to eliminate alternative explanations for the finding.

The external validity of an RCT refers to its degree of generalizability, that is the level the outcome of the study can be expected to apply to a broader group of people or other settings. The external validity is crucial for clinical usefulness of the study.

People with disabilities are largely underrepresented in RCTs due to explicit exclusion to the trials or because of inaccessible research protocols (Taylor 2012, Humphreys 2015).

The theme of exclusion of people with intellectual disability or psychiatric disorders has been analyzed in scientific literature.

Taylor (2012) noticed that persons with cognitive impairment were commonly excluded from research in geriatrics either because of discouraging recruitment methods or because of explicit exclusion criteria.

Humphreys (2015) found a high percentage of most-widely cited RCTs that used exclusion criteria that

definitively or possibly precluded the recruitment of persons with psychiatric disorders.

Shepherd (2019) identified in ISRCTN registry only a small number of UK clinical trials including adults who lack capacity to consent to research.

The problem is accentuated in trials for new drugs promoted by pharmaceutical companies because they adopt a greater number of exclusion criteria (Humphreys 2005).

The recurrent arguments adducted for excluding people with psychiatric disorders or intellectual disability from medical research are the potential vulnerability to exploitation and abuse and to coercive pressures, the frequent inability to give informed consent and a higher risk of harm due to a possible exacerbation of the psychiatric disorder during the study (Taylor 2012, Humphreys 2015). Other problems that preclude inclusion are related to researchers rather than people with disabilities (PWDs): lack of confidence in assessing with PWDs with difficulties in communication and collaboration, underestimation of their abilities and attitudes and lack of willingness to make changes in the study project (Feldman 2013).

We analyzed the exclusion rate of persons with intellectual disability or psychiatric disorders in interventional RCTs about the first 10 most frequent causes of disability-adjusted life-years in the world, present in the ClinicalTrials.gov database, started between June 2010 and June 2020.

## METHODS

The search strategy started looking for the Leading 20 Level 3 causes of global DALYs (disability-adjusted life-years) in males and females lists according to the Global Burden of Disease Study (GBD) published on The Lancet on September 2018.

The first 10 causes present in both lists were considered.

Search for RCTs was done utilizing the website Clinicaltrials.gov; the completed, interventional clinical trials with results, with start study date between 06/30/2010 and 06/30/2020 were selected, using the 10 causes of DALYs as key words (a total of 2809 studies).

The first purpose of the study was to assess the proportion of trials in which having intellectual disabilities or psychiatric disorders was an explicit exclusion criterion.

Another goal was to assess the proportion of trials with exclusion criteria that could indirectly lead to the exclusion of people with intellectual disabilities or psychiatric disorders.

The trial characteristics analyzed were:

- Number of study participants.
- Age eligible for study.
- Type of clinical trial: therapeutic (pharmacological, surgical and non pharmacological and non surgical interventional trial) or diagnostic trial.
- Masking: unblinded or blind.

The selected explicit exclusion criteria were:

- Cognitive impairment.
- Behavioural and psychiatric disorders.
- Inability to grant informed consent.

Other exclusion criteria that could be correlated with disability were considered implicit exclusion criteria and included comorbidities or phrases like “Any condition undesirable” or similar and “Depending on the judgement of the researcher”.

The correlation between explicit exclusion criteria and purpose of the study was classified, based on the objective possibility to assess the primary purpose of the study with PWDs, as absolute, relative or questionable. The implicit exclusion criteria were automatically classified as questionable for their lack of specificity. Studies were evaluated by a single researcher but discussed collectively in doubtful cases.

## RESULTS

A total of 2809 studies in the 10 selected categories were reviewed: 260 (9.3%) in “Chronic Ischaemic Heart Disease”, 208 (7.4%) in “Congenital Defects”, 351 (12.5%) in “Chronic Obstructive Pulmonary Disease” (COPD), 1273 (45.3%) in “Diabetes”, 70 (2.5%) in

“Diarrhoea”, 124 (4.4%) in “Headache”, 107 (3.8%) in “Low Back Pain”, 76 (2.7%) in “Neonatal Disorders”, 104 (3.7%) in “Pneumonia” and 236 (8.4%) in “Stroke”.

An average of 487 participants took part in the studies (max 94321, min 1, standard deviation 2370).

The average study start date was 2012 (median 2013).

Of the studies examined, 175 (6.2%) involved participants under 18 years of age, 2462 (87.2%) involved participants over 18 years of age and 172 (6.1%) had a sample of both minors and adults.

With regard to the type of studies, 1812 (64.5%) were pharmacological interventional studies, while the remaining 997 (35.5%) included 137 (4.9%) diagnostic, 65 (2.3%) surgical and 795 (28.3%) classifiable as non-pharmacological and non-surgical interventional RCTs.

The studies were blinded in 1556 (55.4%) cases, while no masking was present in the remaining 1253 (44.6%) studies.

### *Among the explicit exclusion criteria:*

“Cognitive impairment” was present in 488 (17.4%) studies in total, of which 195 (39.9%) were pharmacological, and it was considered an absolute exclusion criterion in 10 studies (2%), relative in 459 (94%) and questionable in 19 (4%). “Behavioural and psychiatric disorders” was present in 616 (21.9%) studies in total, of which 373 (60.6%) were pharmacological, and it was considered an absolute exclusion criterion in 9 (1.5%) studies, relative in 594 (96.4%) and questionable in 13 (2.1%). Finally, the criterion “Inability to grant informed consent” was present in 498 (17.7%) studies in total, of which 281 (56.4%) were pharmacological, and it was considered an absolute exclusion criterion in 9 (1.8%) studies, relative in 471 (94.6%) and questionable in 18 (3.6%).

The three explicit criteria were present, alone or in combination, in 1076 studies (38.3%).

Implicit exclusion criteria were present in 1233 (43.9%) studies.

## DISCUSSION

A growing number of studies highlight the problem of the frequent exclusion of PWDs from randomized clinical trials and such an exclusion does not allow to know if the conclusions of the RCTs are applicable to the specific minority group. The problem must be read and addressed not only from an ethical but also from a practical clinical point of view. The poor representation of people suffering from intellectual disability or psychiatric disorders in scientific studies constitutes social discrimination but also a serious scientific error, since these conditions are frequent and often found in association with other pathologies. The inability to give informed consent was also assessed as it is closely related to mental illness and intellectual disability

(Sheperd 2019). The individual percentages relating to the three explicit categories of exclusion might appear insignificant but, evaluated cumulatively, they reach high and worrying values: more than one study in three contains the explicit exclusion criteria assessed. At the same time, the role of implicit exclusion criteria should be considered, because while they have vague and multifaceted definitions and only to a certain percentage are related to the explicit criteria considered, they are reported so frequently (1233 studies, 43.9%) that their weight could be quite significant. From a methodological point of view, in order to avoid the risk of underestimating the phenomenon, we chose to use the ClinicalTrials.gov database as a source as it provides more detail on the exclusion criteria than is found in scientific articles (Gandhi 2005). One of the strengths of the study is the representativeness of the RCTs analyzed: all the completed, interventional RCTs with results submitted to the ClinicalTrials.gov database concerning issues of major clinical impact worldwide over a long period of time were evaluated. This study shows that although the issue of excluding PWDs from clinical trials has been raised for several years now, there remains a high probability that the most recent scientific research does not reflect the concerns of this group. It is no longer justifiable to ignore the problem or to think that the answer to the difficulties of inclusion is to exclude subjects with comprehension and collaboration difficulties. It is therefore necessary to move swiftly towards an evolution in the way scientific studies are conceived: first and foremost, to proactively assess the possibility of involving subjects with cognitive disabilities and behavioural problems. The concept of Universal Design of Research (UDR), borrowed from architecture, was proposed in the field of scientific research, and brilliantly explored by Williams (2011), with the aim of arriving at research designs that are usable by all, with the greatest possible degree of inclusiveness, without the need for adaptations or modifications for people with disabilities (Williams 2011). It was suggested to think of multiple options to make the study known, to allow access to the study to be carried out and to provide for different ways of communicating information and collecting data from participants. As far as possible, simple equipment and procedures should be used, explained in a sufficiently long time and using easy-to-understand words and methods. Accommodations may also be necessary when a UDR has been applied: these consist of modulations in the way information is presented and data is collected, and in the time allowed for testing.

Finally, it may be necessary to make further changes to the original study design, for example by changing the instrument used to collect the information. Care must be taken with such changes as they may interfere with the internal validity of the study (Rios 2016). In order to clarify the extent to which the results can be

extended to minorities who are often discriminated against, the eligibility criteria and the recruitment process need to be made more explicit (Gandhi 2005, Williams 2011). Only exclusion criteria that have a sound scientific basis and are reasonable for the main objectives of the study should be accepted. A drastic reduction in the generic and excessively broad wording of the exclusion criteria would then make it possible to minimize the researcher's margins of discretion, thereby promoting transparency.

## CONCLUSIONS

Increasing evidence of the underrepresentation of people with psychiatric disorders or intellectual disabilities in RCTs, with the negative consequences described above, should prompt researchers to make serious changes in the way research designs are constructed and agencies responsible for monitoring the quality of scientific research to explicitly request such changes.

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**Contribution of individual authors:**

All Authors have worked together and contributed equally to this manuscript.

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